REMARKS

Applicants respectfully request reconsideration of the rejections set forth in the Final Office Action mailed on November 15, 2002. Claims 1-3, 5-9, 11-13, 15-17,19-21, 24-29, and 44-47 have been rejected. Claims 1-3, 5-9, 11-13, 15-17, 19-21, and 24-29 have been cancelled herein.

Claims 44-47 have been amended so as to be in independent form. Applicants maintain that this amendment adds no new matter and request that it be entered. Claims 44-47 remain pending.

A clean version of the amended claims with instructions for entry pursuant to 37 C.F.R. §1.121(c)(1)(i) is included above. A marked-up version of the amended claims pursuant to 37 C.F.R. §1.121(c)(1)(ii) is attached as Appendix I.

This amendment is to expedite prosecution and should not be construed as acquiescence in any ground of rejection. The comments in the Office action are now addressed in turn.

Specification

The Specification has been objected to for the use of the trademark TWEEN in the application. The Office requests that the mark be capitalized wherever it appears and that it be accompanied by the generic terminology. Applicants acknowledge the objection and elect to defer response until one or more claims in the application are deemed allowable. At that time, Applicants will submit a substitute specification wherein the trademark TWEEN is dealt with appropriately.

Rejections under 35 U.S.C. § 112

Claims 1-14 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. More specifically, the Office has expressed concerns regarding "the quantity or purity of calcium phosphate" required in the claimed invention as well as the nature, volume and/or molarity of the "suitable buffer". Applicants traverse this rejection.

The test for enablement is whether one reasonably skilled in the art can make or use the invention from the disclosure in the application, coupled with information known in the art without *undue experimentation*. *In re Wands*, 8 U.S.P.Q.2d, 1400, 1404 (Fed. Cir. 1988). A considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction

in which the experimentation should proceed. For example, the issue in the *Wands* was whether the specification of the *Wands* patent enabled production of a class of antibodies having IgM isotype and a binding affinity of at least 10^9 M^{-1} using Kohler/Milstein technology. Kohler/Milstein technology is a classical technique that involves individualized screening of hybridomas to identify a subset with desired binding characteristics. Until the hybridomas have been screened, it is unpredictable which will have the desired characteristics. Nevertheless, the court found that "practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody" (858 F.2d at 740). The *Wands* patent was held to be enabled.

Here, the Examiner contends that the specification fails to describe what quantity or purity of calcium phosphate is require or what is considered a "suitable buffer" for use in the claimed invention. Applicants disagree.

As noted in the claims and in the specification, two types of buffer are utilized in the claimed methods. First, a "blocking buffer" is used. According to the specification, a suitable blocking buffer is capable of complexing with any of the particulate material not complexed with the protein being isolated. The specification further indicates that a preferred blocking buffer comprises milk. As such, the specification provides both a functional definition and specific examples of suitable blocking buffers.

The second type of buffer is a "wash buffer" that is used to wash the granular calcium to remove impurities. A suitable wash buffer is any of the standard buffers that are well known in the art. For example, the Alaska patent cited by the Office teaches the use of a sodium phosphate pH 6.8 buffer for washing the hydroxyapatite column. Other suitable wash buffers include any of the standard tris buffers, e.g., Tris/HCL, 1 M solution, available at pH 7.0 , 7.5, or 8.0 from Amersham Biosciences; or 2 M Tris, available for USB Corporation.

A practitioner could readily test a variety of commercially available buffers to identify which one would be optimal for the particular system being used. As noted in the specification, the claimed assay can be readily performed in a high throughput format, thus, allowing screening of many different buffers simultaneously. The examples included in the specification are drawn to the simultaneous testing of 10 samples. Moreover, this type of high throughput assay was routinely performed in the art at the effective filing date of the invention.

Although it may be unpredictable whether one specific buffer would be effective in removing impurities while still allowing the protein to remain complexed to the calcium granules, it is virtually certain that if the practitioner screened a few dozen buffers at varying concentrations, as would be possible in a single micro-titer dish, he or she would be successful in

identifying a reasonable number of buffers suitable for use in the claimed invention. As is apparent from the *Wands* case, those in the art are prepared to perform high-throughput screens of this nature to identify buffers with the desired properties. It is respectfully submitted that the law requires no more.

Similarly, with regard to the use of granular calcium in the claimed assay, Applicants maintain that it would not be an undue burden for one of skill in the art to identify the quantity or purity of calcium phosphate that is most suitable for use in the claimed invention. As indicated in the specification, a suitable calcium phosphate for use in the invention is the form widely used in transformation experiments to allow the introduction of DNA into a living cell, wherein it causes the precipitation of DNA. Such transformation experiments using calcium phosphate are described in, for example, Short Protocols in Molecular Biology, 2nd Edition, Ausubel et al. Editors, John Wiley & Sons, 1992 or Claudio (1992) Methods in Enzymology, 207:391. Moreover, as stipulated in the claims, the calcium phosphate is solid, non-buoyant, and has free ionic valencies. Again, the nature of the calcium phosphate is both functionally and specifically described in the Specification. As such, it would not constitute undue experimentation to identify the quantity or purity of the calcium phosphate.

Applicants maintain that the specification is enabled as to make and/or use the claimed invention. Applicants respectfully request that the rejection be withdrawn.

Rejections under 35 U.S.C. §112, Second Paragraph

Claims 44-47 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point and claim the invention. The Office has expressed concerns regarding the phrase "such as". Applicants have amended the claims herein to address the Office's concerns. Applicants request that the rejection be withdrawn.

Rejections under 35 U.S.C. § 103

The Examiner has maintained the rejection of Claims 1-21, 24-33, and 37-43 under 35 U.S.C. 103(a) as being unpatentable over Schenk et al. U.S. Patent No. 5,593,846 ("Schenk") in view of Alaska et al. U.S. Patent No. 5,744,587 ("Alaska") and Chu et al. U.S. Patent No. 4,604,208 ("Chu"). Claims 44-47 are free of the art.

The teachings of these references have been discussed and distinguished from the present invention in Applicants's previous response. Applicants would like to address the Office's statement that one would have a high expectation of success in the use of hydroxyapatite as compared to calcium phosphate granules, as claimed herein.

As is known in the art, hydroxyapatite is $3Ca_3(PO_4)_2Ca(OH)_2$, the mineral constituent of bone, consisting of needles arranged in a rosette that are practically insoluble in water and decompose above 1100°C. It is also largely insoluble in acid or EDTA. Hydroxyapatite has previously been used to purify and concentrate viruses and their related soluble antigens. However, as noted by Applicants, hydroxyapatite has limited application in the clinical diagnosis of human and animal diseases. Use of granular calcium phosphate (as according to the claimed method) overcomes some of the difficulties found in the use of hydroxyapatite. Moreover, Applicants have found that granular calcium phosphate binds proteins and viruses at a wider range of pH (4-9) as compared to poor results obtained with hydroxyapatite. Accordingly, Applicants maintain that the claimed invention would not have been obvious from the prior art which, at most, teaches the use of hydroxyapatite to remove protein contaminants from a solution.

To expedite prosecution of this patent application and to further the business interests of the Applicant, Applicants have cancelled Claims 1-21, 24-33, and 37-43. As the rejection is now moot, Applicants request that it be withdrawn.

Conclusion

The Applicant respectfully maintains that all pending claims are in condition for allowance. Therefore, the Applicant respectfully requests a Notice of Allowance for this Application from the Examiner. Should any unresolved issues remain, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,
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MARKED UP VERSION OF AMENDED CLAIMS

44. (Amended) A method [of according to claim 9] **of monitoring a liquid for the presence of disease modified or associated proteins, comprising the steps of:**

(a) contacting a sample with solid, non-buoyant granular calcium phosphate having free ionic valencies so as to concentrate said disease-modified or associated proteins in said sample, and

(b) monitoring the resulting disease-modified or associated proteins concentrated on said granular calcium phosphate,

wherein said monitoring step includes amplifying DNA associated with said concentrated protein material using a polymerase chain reaction and then monitoring said concentrated protein material by a restriction fragment length method and, wherein said monitoring step further includes using said amplified DNA material in a **Southern blotting** hybridization **assay** [reaction such as Southern blotting].

45. (Amended) A method [according to claim 1,] **of monitoring a liquid for the presence of disease modified or associated proteins, comprising the steps of:**

(a) contacting a sample with solid, non-buoyant granular calcium phosphate having free ionic valencies so as to concentrate said disease-modified or associated proteins in said sample, and

(b) monitoring the resulting disease-modified or associated proteins concentrated on said granular calcium phosphate, and

wherein said monitoring step further includes using said amplified DNA material associated with said concentrated protein material in a **Southern blotting** hybridization **assay** [reaction such as Southern blotting].

46. (Amended) A method [of according to claim 29,] **of monitoring a liquid for the presence of biological material selected from the group consisting of disease-modified or associated proteins, a fragment thereof, a virus or a fragment thereof, comprising the steps of:**

(a) providing a sample of said liquid;

(b) passing said sample through a solid filter medium having free ionic valencies so as to complex at least one of said biological material to said medium; and

(c) monitoring at least a part of said complexed biological material,

wherein the presence of at least a part of said biological material is indicative of an association of said liquid with the relevant disease,

wherein said monitoring step includes amplifying DNA associated with said complexed biological material using a polymerase chain reaction and then monitoring said complexed biological material by a restriction fragment length method, and

wherein said monitoring step further includes using said amplified DNA material in a **Southern blotting** hybridization **assay** [reaction such as Southern blotting].

47. (Amended) A method [according to claim 19,] **of monitoring a liquid for the presence of biological material selected from the group consisting of disease-modified or associated proteins, a fragment thereof, a virus or a fragment thereof, comprising the steps of:**

(a) providing a sample of said liquid;

(b) passing said sample through a solid filter medium having free ionic valencies so as to complex at least one of said biological material to said medium; and

(c) monitoring at least a part of said complexed biological material,

wherein the presence of at least a part of said biological material is indicative of an association of said liquid with the relevant disease,

wherein said monitoring step includes amplifying DNA associated with said complexed biological material using a polymerase chain reaction and then monitoring said complexed biological material by a restriction fragment length method, and

wherein said monitoring step further includes using said amplified DNA material associated with said concentrated protein material in a **Southern blotting** hybridization **assay** [reaction such as Southern blotting].